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11 November 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **SHORT INTERFERING RNA (siRNA) ANALOGUES**

(57) Abstract: The present invention is directed to novel double-stranded short interfering (siRNA) analogues comprising locked nucleic acid (LNA) monomers. Such compounds induces sequence-specific post-transcriptional gene silencing in many organisms by a process known as RNA interference (RNAi). The compounds disclosed herein has improved properties compared to non-modified siRNAs and may, accordingly, be useful as therapeutic agents, e.g., in the treatment of various cancer forms. More particularly, the present invention is directed to siRNA analogues comprising a sense strand and an antisense strand, wherein each strand comprises 12-35 nucleotides and wherein the siRNA analogues comprise at least one locked nucleic acid (LNA) monomer.



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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK2004/000192

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/11 C07H21/04 A61K31/713 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAMADA M. ET AL.: "Effects on RNA interference in gene expression (RNAi) in cultured mammalian cells of mismatches and the introduction of chemical modifications at the 3'-ends of siRNAs" ANTISENSE & NUCLEIC ACID DRUG DEVELOPMENT, MARY ANN LIEBERT, INC., vol. 12, no. 5, October 2002 (2002-10), pages 301-309, XP009006637 NEW YORK, US ISSN: 1087-2906 cited in the application	1-3, 6-11, 13-15, 20, 25-27
Y	the whole document ----- -/-	66

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the International filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

24 September 2004

Date of mailing of the international search report

06/10/2004

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK2004/000192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAYAKAWA Y.: "Toward an ideal synthesis of oligonucleotides: development of a novel phosphoramidite method with high capability" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, JAPAN PUBLICATIONS TRADING CO., vol. 74, no. 9, 2001, pages 1547-1565, XP001161128 TOKYO, JP ISSN: 0009-2673	63,65-67
Y	the whole document	66
A	BRAASCH D.A. ET AL.: "Novel antisense and peptide nucleic strategies for controlling gene expression" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 41, no. 14, 9 April 2002 (2002-04-09), pages 4503-4510, XP002975681 EASTON, PA, US ISSN: 0006-2960 the whole document	
E	WO 2004/042046 A (GRUENENTHAL GMBH (DE); SCHUBERT S; KURRECK J; GRUENWELLER A; ERDMANN V) 21 May 2004 (2004-05-21)  page 46 - page 48; claims 15-27 page 31 - page 38; examples 5,6	1-12, 14-19, 25,27, 28,31, 35,36,50

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK2004/000192

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material

☒

a sequence listing

☐

table(s) related to the sequence listing

b. format of material

☒

in written format

☒

in computer readable form

c. time of filing/furnishing

☐

contained in the international application as filed

☐

filed together with the international application in computer readable form

☒

furnished subsequently to this Authority for the purpose of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK2004/000192

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 48-60, 62 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK2004/000192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004042046 A	21-05-2004	WO 2004042046 A2	21-05-2004